EVALUATION OF CURRENT DOSING PRACTICE OF ATROPINE

&

EVALUATION OF A PROTOCOL OF ATROPINE DOSING IN THE MANAGEMENT OF ACUTE ORGANOPHOSPHORUS POISONING.

A Dissertation submitted in partial fulfillment of **M.D. Branch I (General Medicine)** Examination of **The Tamilnadu Dr. M.G.R. Medical University, Chennai** to be held in **March 2007.**

CERTIFICATE

This is to certify that

"**EVALUATION OF CURRENT DOSING PRACTICE OF ATROPINE, & EVALUATION OF A PROTOCOL OF ATROPINE DOSING IN THE MANAGEMENT OF ACUTE ORGANOPHOSPHORUS POISONING.**"

which is submitted as thesis requirement of the MD General Medicine Branch examination of the The Tamilnadu Dr. M.G.R. Medical University is the bonafide work of the candidate: Dr. Ashish Singh.

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CONTENTS

ABSTRACT

Treatment of OP poisoning includes continuous monitoring and timely intervention, ideally in an intensive care unit and is labour intensive. In our setting where cost is a major factor and a large number of patients who are unable to afford care in an intensive care unit are treated even while they require mechanical ventilation in the general wards, a treatment regimen which is simple, easy to follow and includes fixed guidelines may be more easier, efficient and improve care in situations where ICU care is not possible immediately.

This study attempted to formulate, based on the current practice and evaluate an algorithmic protocol of atropine in the management of moderate to severe acute organophosphate poisoning. The current study shows that use of a guideline may result in faster atropinisation and rapid stabilization of acutely sick patients who are treated initially in the emergency room.

Conclusion: Administration of atropine using a fixed algorithm is easy and effective in providing the atropine requirement in the management of early phase of acute organophosphorus poisoning. Smaller doses of atropine are sufficient in treating cases of OP poisoning, than those recommended in literature. This results in less atropine toxicity, without increasing complications. An algorithmic approach to atropine dosing appears promising.

INTRODUCTION

Organophosphorus poisoning is one of the most common means of attempting suicide in India[1]. This problem seems to be peculiar to India and other south asian countries as most of the compounds are available freely in the market as pesticides for agricultural use. In developing countries more than 90% of acute poisoning is due to suicidal attempt[1]. Most cases occur following occupational or deliberate exposure to organophosphorus pesticides. Although data are sparse, organophosphates appear to be the most important cause of death from deliberate self poisoning worldwide.[2]

Organophosphate compounds inhibit both cholinesterase and pseudo-cholinesterase activities. The inhibition of acetylcholinesterase causes accumulation of acetylcholine at synapses, and the resulting overstimulation of neurotransmission at the neuromuscular junction, disturbs transmission at parasympathetic nerve endings, sympathetic ganglia, neuromuscular endplates and certain CNS regions[25].

Early diagnosis and appropriate treatment is often life saving. The early clinical course of OP poisoning may be quite severe and may need intensive care management. Atropine is the mainstay of treatment of effects mediated by muscarine sensitive receptors.

Therapy requires the urgent use of atropine to reverse cholinergic excess, thereby improving respiratory function, heart rate, and blood pressure.

There is great variation in recommendations in textbooks for adequate dose of atropine[18] and atropinisation of an average patient some times can take hours and even days to stabilize vital parameters.

The dose of atropine is usually individualized to the patient's heart rate, pupil size, respiratory secretions and levels of CNS arousal. The guidelines being variable it is difficult for an inexperienced junior doctor to follow[18]. Mortality following OP poisoning remains high despite adequate respiratory support, intensive care, and specific therapy with atropine especially in the early hours. Significant numbers of the subjects needing mechanical ventilation and reaching intensive care units die within the first 72 h of poisoning. This may be because of failure to stabilize patients early during the course of illness. On the other hand atropine overdose in itself may be responsible for adverse outcome especially in the elderly population.

There is a trend towards using minimum doses of atropine and avoiding Oximes altogether as their efficacy is still controversial* and their use late in the illness may not be useful. The optimum atropine dosage is not yet defined and under or overdosing with atropine is a common occurrence for sick patient presenting to emergency room.

The present study was chosen to study the existing pattern of atropine administration in the treatment of acute organophosphate poisoning. It was felt that the knowledge gained by the study would allow the development of a simple protocol for atropine administration prospectively.

The new simplified protocol should be easy to administer, should be effective in blocking the clinical effects of muscuranic stimulation without causing atropine toxicity. And should be able to speed up the initial time needed to stabilize a patient by achieving rapid atropinisation, and provide a regular dose in the form of infusion which is easy to administer and more physiological.

AIMS

The aim of the study is to evaluate the atropine dosing pattern currently in practice at the Department of general medicine, Christian Medical College and Hospital, Vellore; and thereafter to develop and evaluate a simple algorithm for atropine administration in the treatment of acute organophosphate poisoning.

OBJECTIVES

i) To study the dose requirement of atropine, for initial adequate atropinisation and subsequent requirement in the treatment of acute organophosphorus poisoning (Part I).

ii) To develop a simple algorithmic dose regimen of atropine using the results of the Part I study in treatment of acute organophosphate poisoning (Part II).

iii) To study the feasibility, safety, effectiveness and complications of the algorithmic dose regimen developed as above (Part II).

REVIEW OF LITERATURE

Acute organophosphorus (OP) poisoning is a common problem in the developing countries [1,2]. It probably kills about 300,000 people every year [3,4]. Most deaths occur in the rural areas of the developing world [2]. In countries like India deliberate self poisoning is the most common cause of death second to road traffic accidents [5]. Their widespread use as insecticides and easy availability has resulted in serious increase in poisoning. The extent of acute pesticide poisoning in agricultural workers, particularly in less developed countries, has often been based on inadequate information. Epidemiological studies, relying mainly on hospital and poison centre data, have been biased towards the more severe poisonings, whereas field studies indicate that occupational pesticide poisoning is associated with less severe and minor effects. Many reports do not adequately distinguish between intentional, accidental and occupational pesticide poisoning statistics or are dominated by cases of intentional poisoning which, by their nature, result in severe or fatal results.

Epidemiology:

World health organization estimates suggest that more than 3 million cases of acute serious pesticide poisoning and 220,000 deaths occur worldwide annually, the majority being caused by organophosphates used for

agricultural purposes [1]. In the hospital based poisoning surveys from India 59% of all admissions are due to pesticide poisoning[6].

In the Christian Medical College and Hospital, Vellore OP poisoning accounts for 12% of all medical intensive care unit admissions and 75% of all poisoning [7]. In a recent study by Srinivas Rao et al from India there were 8040 admissions in 6 years with an overall case fatality ratio of 22.6%, two thirds of these were less than 30 years old, with 96% rates of intentional poisoining[8] .

History:

The first OP compound synthesized by Clermont in 1854 was tetraethyl pyrophosphate (TEPP). It came into use during World War II as an agricultural pesticide substitute for nicotine and for use as a nerve gas in chemical warfare. It is also the most toxic of the OP insecticides. Modern investigations of OP compounds date from the 1932 publication of Lange and Krueger on synthesis of dimethyl and diethyl phosphoflouridates. Schrader described the structural requirements for insecticide activity of these compounds in 1952.

Pathophysiology of organophosphorus poisoning:

The primary mechanism of action of OP pesticides is inhibition of acetylcholinesterase (AChE), which is an enzyme found in the nervous system. Its normal action is to break down acetylcholine (ACh).

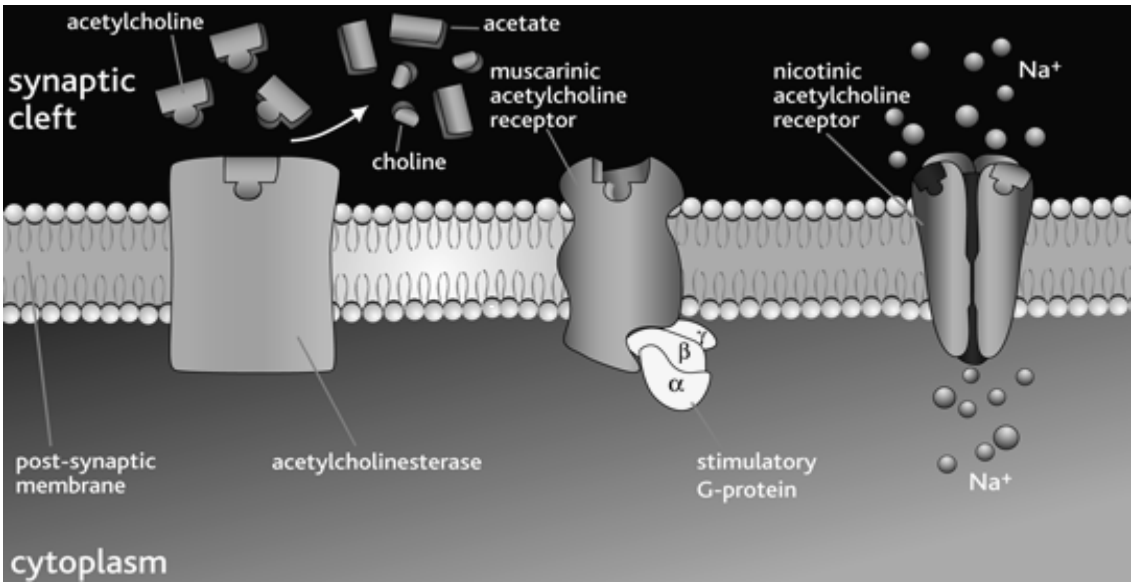


Figure 1: Action of acetylcholinesterase

OPs inactivate AChE by phosphorylating the serine hydroxyl group located at the active site of AChE. The phosphorylation occurs by loss of an OP leaving group and establishment of a covalent bond with AChE. Once AChE has been inactivated, ACh accumulates throughout the autonomic ervous system, the somatic nervous system, and the brain, resulting in overstimulation of the muscarinic and nicotinic receptors.

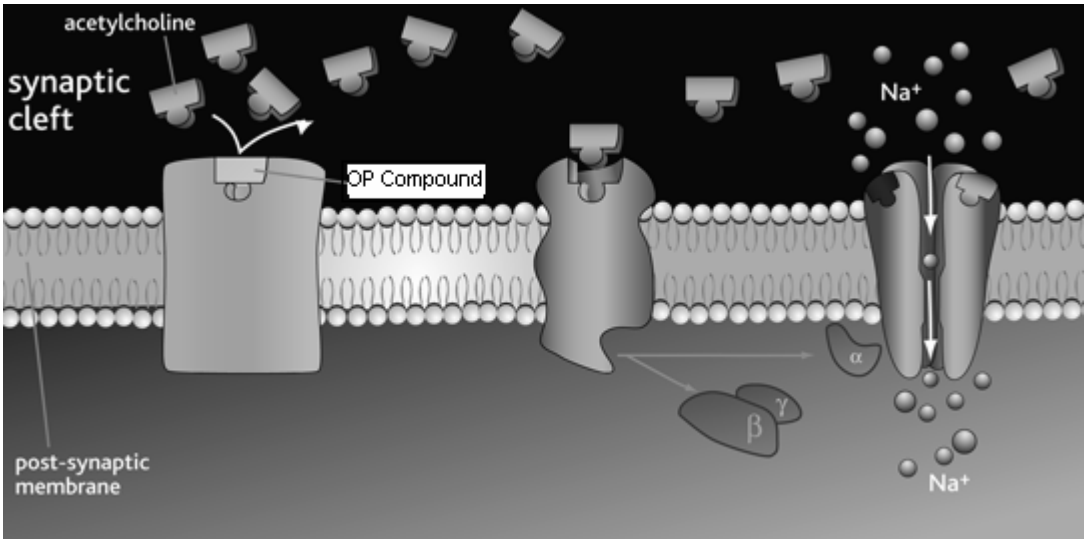


Figure 2: Inactivation of AChE and accumulation of ACh in the synapse.

(Figures r*eproduced from;* Pharmacology, *4th edition. Rang HP, Dale MM and Ritter JM. Edinburgh, UK: Harcourt Publishers Ltd, 2001:110–138.)*

The preganglionic and postganglionic neurons in the parasympathetic nervous system release ACh. Postganglionic ACh acts on muscarinic receptors on the heart, eyes, glands, GI tract, and respiratory system. Somatic motor axons emerge from the spinal cord and directly innervate muscle cells at the neuromuscular junction, releasing ACh on nicotinic receptors. The brain and spinal cord both contain muscarinic and nicotinic receptors. Cholinergic pathways in the brain are associated with various behaviors and functions, including hunger, thirst, thermoregulation, respiration, aggression, and cognition.

Once an OP binds to AChE, the enzyme can undergo 3 processes, including

(1) Endogenous hydrolysis of the phosphorylated enzyme by esterases or paraoxonases,

(2) Reactivation by a strong nucleophile such as pralidoxime (2-PAM), and

(3) Biological changes that render the phosphorylated enzyme inactive (aged).

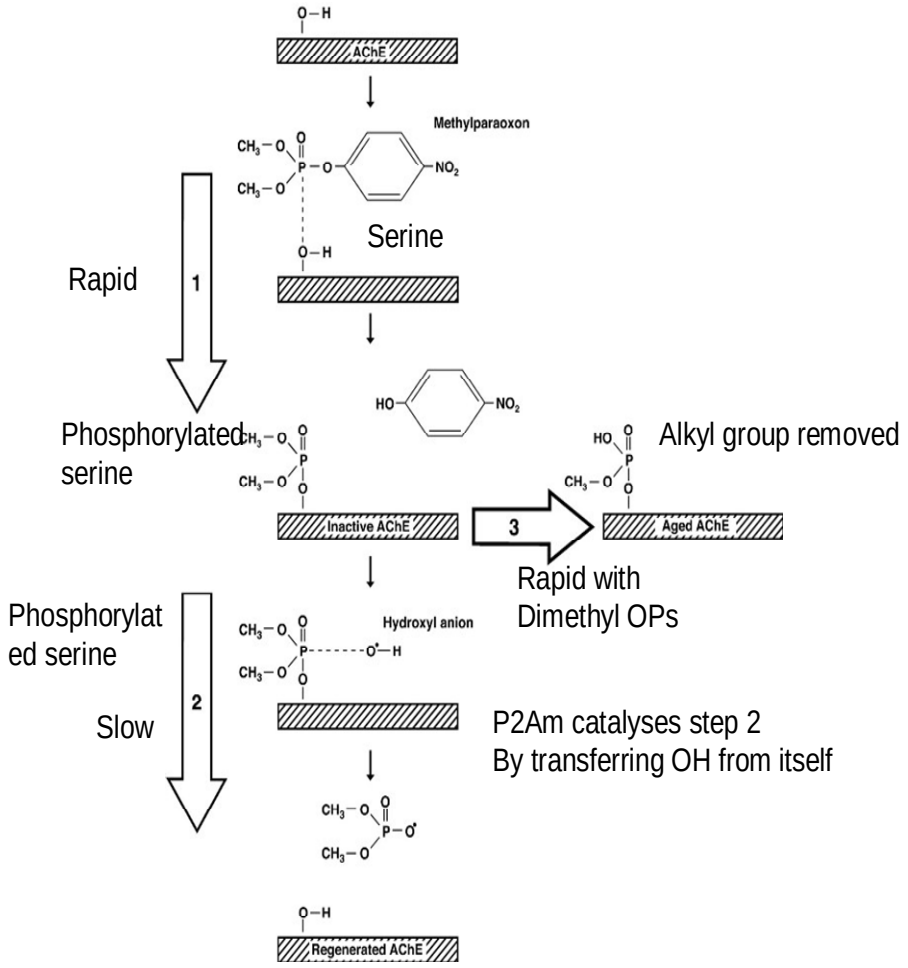


Figure 3: Interactions between OP compound and AChE enzyme.

OPs can be absorbed cutaneously, or they can be ingested or inhaled. Onset and duration of action depend on the nature and type of compound, the

degree and route of exposure, the mode of action of the compound, lipid solubility, and rate of metabolic degradation.

Clinical manifestations:

The signs and symptoms of acute organophosphate poisoning are due to the effects caused by excess acetylcholine (cholinergic syndrome); they can manifest at different times. Signs and symptoms can be divided into three groups:

- Muscarinic effect: parasympathetic.
- Nicotinic effect: sympathetic and motor.
- Central nervous system effect: M1 muscuranic receptor stimulation.

The clinical syndrome of organophosphorus poisoning can be classified into

1. Acute manifestations: The cholinergic phase (occurs within 0-24 hrs.).
2. Intermediate syndrome: Due to persistent nicotinic effects of acetylcholine excess (Develops 24 to 96 hours after resolution of acute cholinergic symptoms and may persist for 4 to 18 days)
3. Chronic manifestations: Delayed neurotoxicity due to axonal degeneration.

(Occurs 2-3 weeks after exposure to large doses and recovery may take upto 12 months.)

According to the degree of the severity of poisoning, the following signs and symptoms can occur during the acute phase [11,12].-

*Mild: anorexia, headache, dizziness, weakness, anxiety, substernal discomfort, fasciculations of the tongue and eyelids, miosis, and impairment of visual acuity.

*Moderate: nausea, salivation, bronchorrhoea, lacrimation, abdominal cramps, diarrhoea, vomiting, sweating, hypertension or hypotension, and muscular fasciculations.

*Severe: miosis or mydriasis, non-reactive pupils, dyspnoea, respiratory depression, pulmonary oedema, cyanosis, loss of sphincter control, convulsions, coma, bradycardia or tachycardia, cardiac ischaemia, cardiac dysrhythmias, hypokalaemia, and hyperglycaemia. Acute pancreatitis has also occurred. Muscular paralysis may involve the respiratory muscles.

Muscarinic effects by organ systems include the following:

Cardiovascular - Bradycardia, hypotension

Respiratory - Rhinorrhea, bronchospasm, bronchorrhea, cough

Gastrointestinal - Increased salivation, nausea and vomiting, abdominal pain, diarrhea, and fecal incontinence

Genitourinary - Urinary incontinence

Ocular - Blurred vision, miosis

Glands - Increased lacrimation, increased sweating

Nicotinic signs and symptoms include muscle fasciculations, cramping, weakness, and diaphragmatic failure. Autonomic nicotinic effects include hypertension, tachycardia, pupillary dilation, and pallor.

CNS effects include anxiety, restlessness, confusion, ataxia, seizures, insomnia, dysarthria, tremors, and coma.

Neurological manifestations:

Type I - Acute paralysis secondary to persistent depolarization at the neuromuscular junction.

Type II (intermediate syndrome) - Intermediate syndrome was described in 1974 by Wadia et al [13], with an incidence from 8-49%. It develops 24-96 hours after resolution of acute cholinergic poisoning symptoms and manifests commonly as paralysis and respiratory distress. This syndrome involves proximal muscle groups, with relative sparing of distal muscle groups. Various degrees of cranial nerve palsies also are observed. Neuromuscular transmission defect and toxin-induced muscular instability play a role in intermediate syndrome. Intermediate syndrome persists for 4-18 days, can require intubation, and can be complicated by infections or cardiac arrhythmias.

Type III - Organophosphate-induced delayed polyneuropathy (OPIDP) occurs 2-3 weeks after exposure to large doses of certain OPs. Distal muscle weakness with relative sparing of the neck

muscles, cranial nerves, and proximal muscle groups characterize OPIDP. Recovery can take up to 12 months.

Death in severe poisoning is likely due to effects on heart (bradycardia, arrythmias and hypotension), respiration (central or peripheral respiratory failure) and on the brain (depression of vital centres)[9].

The mechanism of cardiac toxicity is unclear and the following have all been postulated:

1. A direct toxic effect on the myocardium
2. Overactivity of cholinergic or nicotinic receptors causing haemodynamic alteration
3. Hypoxia
4. Acidosis
5. Electrolyte abnormalities
6. High dose atropine therapy. (used as treatment for organophosphate poisoning).

Management:

The following are the major aspects in the management of patients with acute organophosphorus poisoning. Despite the large number of pesticide poisoning cases occurring worldwide every year, the current evidence base in the management of acute organophosphorus poisoning is small [28].

1. Asses breathing and circulation.
2. Ensure adequate airway – suction of copious secretions and vomitus.

3. Ensure adequate oxygenation and ventilation.
4. Anticholinergic drugs – atropine.
5. Hemodynamic resuscitation.
6. Removal of contaminated clothing (in cases of accidental exposure or spilling over body).
7. Skin and mucus membranes decontamination.
8. Control of convulsions.
9. Monitoring of heart rate, blood pressure, oxygenation and level of consciousness.
10. Gastric lavage.
11. Oximes.
12. Active cooling and sedation.

Gastric decontamination

1. Ipecacuanha has been used to induce emesis in poisoned patients. It takes 20-30min to work and vomiting may last for more 30min[23]. If loss of consciousness occurs during this time, intubation may be needed in an unconscious vomiting patient. Since patients with pesticide poisoning may suddenly deteriorate, ipecacuanha is contraindicated. Forced emesis in hospital using other techniques is ineffective[23].

2. Gastric lavage is a routine practice in most cases of organophosphorus poisoning by oral route. The efficacy of gastric lavage falls rapidly with time since ingestion[24]. By the time most patients arrive in hospital, the

majority of pesticide will have passed into the small bowel, out of the reach of gastric lavage. Some diluted solvent may be left in the stomach – this will smell of 'pesticide' if sucked out with a NG tube. The volume of fluid in the stomach will appear large in cholinergic poisoning due to the secretion of fluid into the bowel[25]. However most of the hospital practices gastric lavage even up to 4-6 hours after thy intake of poison.

3. Activated charcoal is routinely advocated to "adsorb" ingested poison.

There is currently no evidence that either single or multiple dose regimens of activated charcoal result in clinical benefit[26,27].The practice of giving charcoal rests upon usual practice and is now being evaluated in an RCT (ISRCTN02920054).

Giving fluids:

There have been no studies on the effects of giving IV fluids in ill patients with OP poisoning. However, due to the cholinergic effects, these patients lose a great deal of fluid into their gastrointestinal tract and lungs, and onto their skin as sweat, resulting in intravascular fluid depletion. Some also develop severe diarrhea that results in fluid and potassium loss[14].

There is no evidence that giving fast IV fluid to patients with bronchorrhoea is dangerous as long as atropine is being given simultaneously to dry the lung secretions.

Oximes:

Oximes reactivate the acetylcholinesterase by removing the phosphoryl group (reaction 2, figure1). Pralidoxime is the enzyme which is used most commonly worldwide. It occurs in two common forms: Pralidoxime chloride (2-PAM, molecular weight 173) and Mesylate(molecular weight 232).

In the following situations however reactivation of inhibited acetylcholinesterase will be absent or limited.

1. Poor affinity of the OP-AchE complex.
2. Insufficient dose or duration of treatment.
3. Persistence of the OP within the patient and hence rapid reinhibition of newly reactivated enzyme.
4. Ageing of the inhibited acetylcholinesterase.(reaction 3, figure 1).

The clinical benefit of oximes for OP pesticide poisoning is not clear, being limited by the type of OP, poison load, time to start of therapy, and dose of oxime [29,30]. Current World Health Organisation guidelines recommend giving a 30 mg/kg loading dose of pralidoxime over 10–20 min, followed by a continuous infusion of 8–10 mg/kg per hour until clinical recovery or 7 days, whichever is later [30,31]. However assessment of the primary outcomes in a recent meta-analysis indicated either a null effect or a tendency of harm with oxime therapy[32].

At the Christian Medical College Vellore the practice of using oximes was stopped from 1999 following the results of studies reported in literature about a tendency of harm with oximes. The data during the “no oxime era” (1999-2005) for patients admitted in the adult medical intensive care unit is shown[38].

Year	Total patients	OP poisoning (% of total admission)	Mortality of OP (%)
1999	758	111 (14.6)	15 (13.5)
2000	787	118 (15.0)	17 (14.4)
2001	790	112 (14.2)	19 (17.0)
2002	759	99 (13.0)	14 (14.1)
2003	735	102 (13.9)	15 (14.7)
2004	697	101 (14.5)	14 (13.9)
2005	702	82 (11.7)	12 (14.6)

Table 1: Mortality in OP poisoning of patients treated in ICU.

The above data can be taken only as a benchmark for the mortality in patients without the use of oximes. It can not be compared with the earlier mortality during the oxime usage era, because the decline in mortality is probably multifactorial, including the improved standard of care in the medical intensive care unit over this period of time.

The lack of current prospective randomized controlled trials, with appropriate patient stratification, mandates ongoing assessment of the role of oximes in organophosphate poisoning.

Active cooling and sedation:

Hyperthermia is a serious complication in hot and humid wards. A febrile patient should receive the minimum amount of atropine needed to control muscarinic signs, sedation if there is excessive agitation and muscle activity, and active cooling.

Reduce agitation with diazepam. Restraining a non-sedated agitated patient to the bed is associated with complications, including death. Such patients struggle against their bonds and generate excess body heat, which may result in hyperthermic cardiac arrest[14].

Diazepam is preferred over haloperidol because large doses of haloperidol may be required in patients receiving atropine. Haloperidol is also non-sedating, associated with disturbances of central thermoregulation and prolongation of the QT interval, and pro- convulsant. Diazepam may also have other advantages because animal studies suggest that it reduces damage to the central nervous system[33] and diminishes central respiratory failure[34].

Anticholinergic drugs:

Atropine is a specific antidote for the treatment of poisoning with organophosphorus and carbamate insecticides and organophosphorus nerve agents.

Atropine is the best-known member of a group of drugs known as muscarinic antagonists, which are competitive antagonists of acetylcholine at muscarinic receptors. It has no effect at the nicotinic receptors. This naturally

occurring tertiary amine was first isolated from the *Atropa belladonna* plant by Mein in 1831. Atropine earlier enjoyed widespread use in the treatment of peptic ulcer, today it is mostly used in resuscitation, anaesthesia, and ophthalmology. It may also be used to counteract adverse parasympathomimetic effects of pilocarpine, or neostigmine administered in myasthenia gravis. The first report of atropine being used as an antidote for acetylcholinesterase inhibitors was by Fraser in 1870, he used atropine to counteract the effect of physostigmine on the pupil. Sanderson in 1961 described the effect of intraperitoneally administered atropine given alone, or combined with oximes, on the survival of rats poisoned by organophosphates[11].

Textbooks list many features of the cholinergic syndrome [11,12] . However, in practice mainly the following five are used in routine assessment: miosis, excessive sweating, poor air entry into the lungs due to bronchorrhoea and bronchospasm, bradycardia, hypotension and fasciculations. If none of these signs are present, then the patient does not yet have clinical cholinergic poisoning and does not require atropine. Fasciculations are due to the depolarizing blockade at the neuromuscular junction as stated earlier, atropine does not reverse fasciculations. However, it is possible that these signs will occur later, for example as a pro-poison (thion) OP is converted to the active oxon form, as a fat-soluble OP such as fenthion leaches out of fat stores into the blood, or if the patient has presented soon after the ingestion. Careful observation is required to look for the development of cholinergic signs.

Giving atropine before oxygen:

Although it is preferable that oxygen is given early to all ill patients, delay should not occur in giving atropine if oxygen is unavailable.

Some reports suggest that atropine should not be given to a cyanosed patient until oxygen has been given - to reduce the risk of atropine inducing ventricular tachycardias[11]. While apparently sensible, such advice risks preventing doctors working in small rural hospitals from giving life-saving atropine treatment, since many do not have oxygen. Furthermore, in treatment of more than 800 patients receiving atropine, many of whom received atropine before oxygen, no patient had a cardiac arrest within minutes of giving atropine[14]. The primary evidence for an increased risk of a ventricular dysrhythmia from giving atropine to a cyanosed patient consists of very few patients. Since atropine dries secretions and reduces bronchospasm, its administration should reduce cyanosis. There is no good evidence that giving atropine to a cyanosed patient causes harm [14].

Use of atropine

Basic pharmacology and animal work suggests that early antagonism of pesticide toxicity should be associated with better outcomes [15,16]. Although there are few studies on the subject, there is some evidence that patients in the developing world often die soon after admission[17]. Full and early atropinisation is an essential and simple part of early management. Delayed atropinisation can result in death from central respiratory depression,

bronchospasm, bronchorrhoea, severe bradycardia and hypotension[25]. Animal work suggests that these early deaths may be primarily due to central cholinergic stimulation[15].

The initial half life of distribution of atropine is about 1 minute[11,22]. After intravenous dosing, atropine distributes rapidly with only 5% remaining in the blood compartment after five minutes. Studies in anesthetized patients indicate that the peak effect is seen within three minutes of an IV injection[23]. There is therefore no need to wait for more than five minutes before checking for a response and giving another bolus dose if no response has occurred. After intravenous dosing, atropine elimination fits a two-compartment model with an intrinsic clearance of 5.9-6.8 ml/kg/min and a plasma half-life of 2.6-4.3 hours in the elimination phase[11]. In an emergency situation, it may be necessary to give atropine before intravenous or intraosseous access can be established. The endotracheal route has therefore been used, when vascular access was not available with success. The best regimen for the administration of atropine has not been established [11]. A study performed in Bangalore, India, found that a regimen of bolus loading doses followed by an infusion improved outcome compared to repeated bolus doses [19] however, this study used historical controls which risks inflating benefit compared to RCTs [20,21]. Although the benefit of infusions is not yet proven, the use of bolus loading doses followed by an infusion may save time, require less observation, produce less fluctuation in plasma atropine concentrations, and make weaning easier [11].

It is preferred to give low doses of atropine to start with and then rapidly escalate the dose. An alternative approach is to start with much bigger doses, to ensure rapid atropinisation, and then wait for the atropine levels to fall. Because of the dangers of over-atropinisation, however, the former practice offer more control by starting with low doses. It is difficult to distinguish patients who needed very large doses of atropine from those who required just a few milligrams[18].

There are various recommendations about the use of atropine in the treatment of organophosphorus poisoning. Eddleston et al *obtained thirty three different recommendations for atropinisation from clinical toxicology textbooks and electronic sources, national formularies, and international textbooks of internal medicine.

The following is the atropine recommendations in text books, handbooks, and online databases of clinical toxicology as published by Eddleston et al in there study on comparison of recommended regimens of atropine[18].

Dose recommended in the literature for atropine in treatment of acute OP poisoning.

Source	Edition/ year	recommendation	Maximum dose 24 hrs	Atropine dose per hour.
Harrisons text book of Medicine	16th/2005	0.5-2mg repeated every 5-15 minutes	192 mgs	8 mgs/hour
Davidsons text book of Medicine	19th/2002	2 mg repeated every 10 minutes	288 mgs	12 mgs/hour
British national formulary	46th/2003	2mgs repeated every 5-10 minutes	576 mgs	24 mgs/hour
Oxford textbook of Medicine	4th/2003	2 mgs repeated every 10-30 minutes	288 mgs	12 mgs/hour
WHO treatment guide	1999	1-2 mgs repeated every 5-10 minutes	576 mgs	24 mgs/hour
Poisindex OP Poisoning	2003	2-5 mgs every 10–30 minutes	720 mgs	30 mgs/hour
Ford	1st/2001	1-2 mgs repeated every 5 minutes doubling the dose.	Large Doses (100s of mgs)	
Reigart	5th/1999	If GCS normal: 2-4 mg every 15 min. If GCS reduced: 4-8 mg every 5-15 minutes.	Large doses.	96 mgs/hour
Fernando	2nd/1998	2-10 mg, then 2 mg repeated every 10-15 minutes	298 mgs.	12 mgs/hour

Table 2: Atropine dose recommendations in literature.

He calculated the time needed to achieve initial atropinisation by using these regimens on his 22 patients enrolled in the study. The patients required a mean of 23.4 mg (standard deviation 22.0, range 1–75 mg) atropine to clear the lungs, raise the pulse above 80 bpm, and restore systolic blood pressure to more than 80 mmHg. Textbook recommendations varied markedly — atropinisation of an average patient, requiring the mean dose of 23.4 mg, would have taken 8 to 1380 mins; atropinisation of a very ill patient, requiring 75 mg, would have taken 25 to 4440 mins. Thus there is great variation in recommendations for adequate dose of atropine. Thus there is a need to review the evidence for atropine administration and to produce and disseminate a simple guideline that will be useful for doctors faced by this severe form of poisoning across the world. Given the paucity of existing evidence, clinical studies looking to determine the optimal dosing regimen of atropine that rapidly and safely achieves atropinisation in these patients are required.

Criteria for atropinisation

Patients die acutely from respiratory or circulatory failure, the former of which is exacerbated by bronchospasm and bronchorrhoea. All respond to atropine treatment.

There are no comparative studies of markers for adequate atropinisation[18]. In particular, since current endpoints do not include a CNS endpoint, it is possible that atropinisation is not reversing the CNS cholinergic syndrome, which may have significant effect on preventing early death from

OP poisoning [15]. In practice, air entry on chest auscultation, heart rate, and blood pressure are the main parameters used for adequate atropinisation. Furthermore, both dilated pupils and tachycardia can result from stimulation of nicotinic ACh receptors, and tachycardia result from low total peripheral resistance with a partially compensatory high cardiac output[35].

In summary the target end point to atropine therapy[14]:

a) Clear chest on auscultation with no wheeze

b) Heart rate >80 beats/min

c) Pupils no longer pinpoint

d) Dry axillae

e) Systolic blood pressure >80 mmHg

Atropine toxicity

There has been a tendency among clinicians to advocate over-atropinisation to reduce the risk of them being under-atropinised. However, atropine toxicity has its risks and complications. Hyperthermia is a particularly serious complication in the hot wards of the developing world. Initial CNS stimulation leads to severe agitation. Agitated patients in ambient temperatures greater than 35C, not sweating because of atropine, can become very hot. Hyperthermia resulting from the high ambient temperatures is exacerbated by intense muscle activity due to atropine-induced agitation and failure of sweating, and sometimes if the patient is an alcoholic, then the situation is worsened due to delirium tremens. Endpoints such as pulse rates

>120/min and totally dilated pupils suggest that the patients are being given too much atropine. A further problem with fast heart rates is ischaemic heart disease in elderly patients. There are reports of patients with fairly mild poisoning who died in ICU from myocardial infarctions after being given atropine to keep their heart rate at 120–140 bpm[18]. Other complication of atropine usage includes paralytic ileus, urinary retention, and precipitation of glaucoma and hypersensitivity reactions[11].

Glycopyrronium bromide (glycopyrrolate)

Glycopyrronium bromide has been used instead of atropine because it is thought to have fewer adverse effects on the central nervous system. There are no randomized controlled trials comparing glycopyrronium bromide (glycopyrrolate) versus placebo, but it is unlikely that such a trial would be considered ethical unless glycopyrronium bromide and placebo were administered in addition to atropine. One small randomized controlled trial found no significant difference in mortality or ventilation rates between glycopyrronium bromide and atropine, but it may have lacked power to detect clinically important differences[37].

Conclusion:

The above review shows that there is a lacuna in information on the requirement of atropine in the management of acute organophosphorus poisoning. Although there are reports of patient being managed with both low and high dose atropine there are no recommendations or human studies or any formulated protocol in the treatment of organophosphorus poisoning.

This study is designed to be a prospective descriptive analysis of the current dosing practice of atropine being used in the department of medicine (Part I).

The data will be used to develop a dosing protocol and this protocol will be prospectively evaluated in the treatment of acute organophosphorus poisoning (Part II).

MATERIALS AND METHODS

The study was performed in two parts, Part I & II.

PART I:

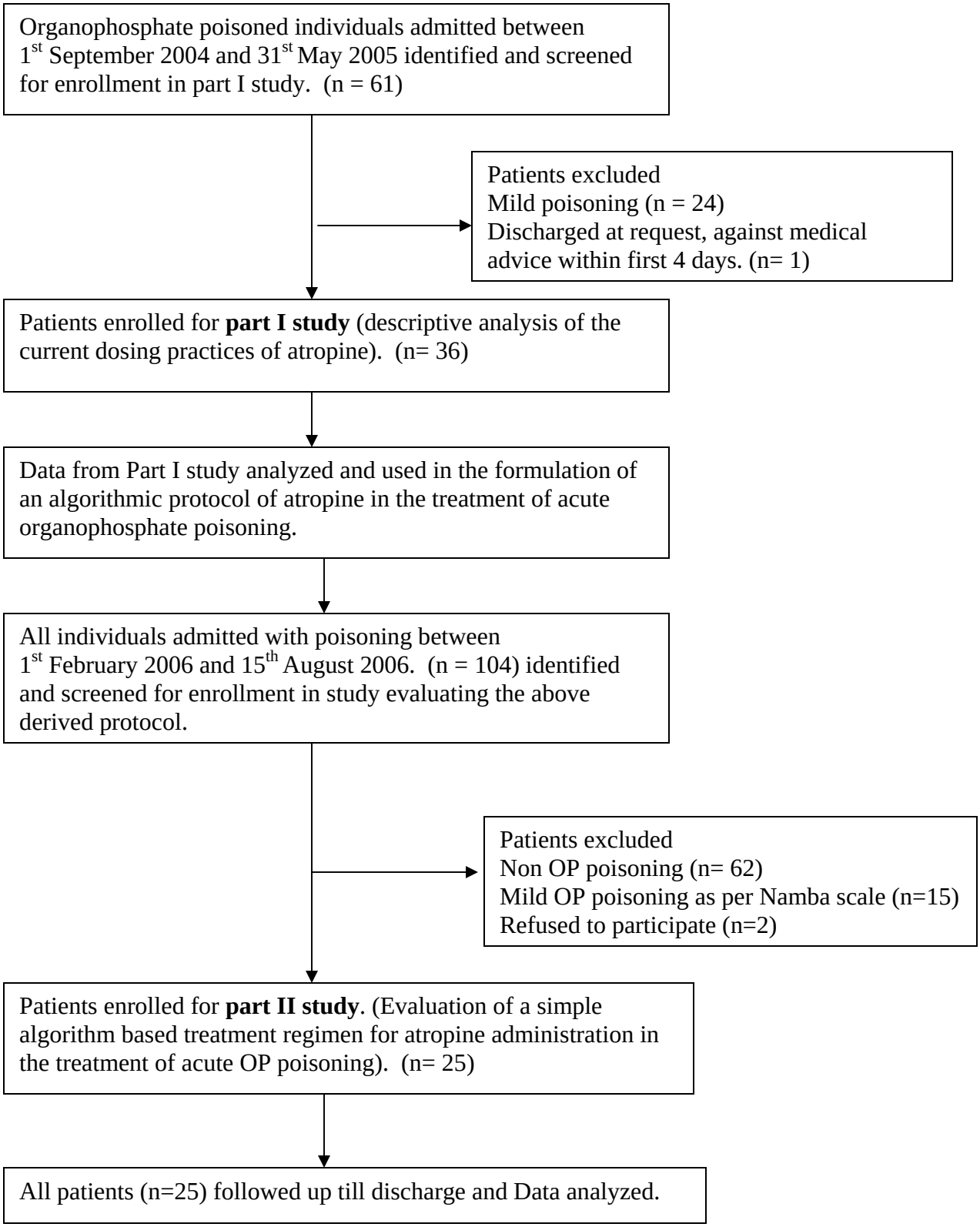
A prospective descriptive analysis of the current dosing practices of atropine at Christian Medical College Hospital Vellore in the treatment of acute organophosphate poisoning and thereafter to develop a simple algorithm based treatment regimen for atropine administration in the treatment of acute organophosphate poisoning.

PART II

A prospective clinical evaluation of a simple algorithm based treatment regimen for atropine administration in the treatment of acute organophosphate poisoned adults admitted to Christian Medical College Hospital Vellore for the treatment of acute organophosphate poisoning.

The study was approved by the research committee of the Christian Medical College Hospital Vellore and a research grant was sanctioned by the committee for the expenses incurred during the study.

STUDY FLOW DIAGRAM



STUDY DESIGN - PART I

A prospective descriptive analysis of the current dosing practices of atropine at Christian Medical College Hospital Vellore in the treatment of acute organophosphate poisoning and thereafter to develop a simple algorithm based treatment regimen for atropine administration in the treatment of acute organophosphate poisoning.

Population studied:

Adult population (aged 12 years or older) with moderate to severe poisoning admitted to the emergency ward of Christian Medical College Hospital Vellore after definite history of organophosphate poisoning or with clinical evidence of organophosphate poisoning within 48 hours of poisoning.

Inclusion criterion:

1. History of organophosphate poisoning (within 48 hours of poisoning.) or
2. Signs of organophosphate poisoning (at least one of the following four signs— brochorrhea, miosis, fasciculation, bradycardia) and
3. Low serum pseudocholinesterase level(less than 25% of normal) with
4. Moderate or severe poisoning(Namba scale).

Exclusion criterion:

1. Admission after 48 hours of poisoning.
2. Carbamate or other poisoning.
3. Patients with mild poisoning assessed by the Namba scale[36] (appendix 1).
4. Patients with known systemic illness like malignancy, chronic lung disease, renal or hepatic failure.
5. Pregnancy.

MATERIALS AND METHODS PART I:

All consecutive patients with organophosphorus poisoning or clinically suspected organophosphorus poisoning who fulfilled the inclusion criterion, admitted to the Christian Medical college hospital Vellore between 1st September 2004 and 31st May 2005 were enrolled into the study. Data was prospectively collected from the inpatient records during their treatment and patients were followed up till discharge from the hospital. Based on the data collected a dosing regimen was evolved for the treatment of acute organophosphorus poisoning. The treatment was carried out as per the current practices in the hospital. All the decisions regarding the treatment of the patient was made by the treating team.

Clinical assessment:

Daily assessment and documentation of the hourly atropine requirement, atropine toxicity, in hospital events, complications, onset of intermediate syndrome, requirement for mechanical ventilation, tracheostomy and duration of mechanical ventilation were documented according to the clinical proforma (Appendix 2) by the investigator till the patient was discharged from the hospital for both parts of the study.

Assessment of severity of poisoning

The severity of poisoning was assessed by the Namba scale[36] (appendix 1). The poisoned patients were divided into three categories, mild, moderate and severe. Only patients with moderate or severe poisoning were included in the study.

Diagnosis of intermediate syndrome:

Intermediate syndrome was defined as proximal muscle weakness of Grade 3 or less, 72 hrs after poisoning with or without requirement of mechanical ventilation.

Markers used to asses' atropine toxicity

Confusion, pyrexia, absent bowel sounds or urinary retention were used mainly in the diagnosis of atropine toxicity. Other possible reasons for the mentioned features were excluded.

Outcome measures

1. Duration of hospital stay was calculated from the time of admission to the discharge of the patient from the hospital, measured in days.
2. Duration of ICU stay: from admission to discharge from medical ICU measured in days.

   The patients are transferred from the medical ICU on the basis of the following criterion

   a. Off ventilatory support for 24 hours

   b. Hemodynamically stable
3. Need for ventilation

The need for ventilation was based on the following guidelines

a. Respiratory rate of more than 30/min.

b. Shallow breathing

c. Oxygen saturation of < 90% or PaO_2 < 60 mmHg or

   PCO_2 > 50 mm Hg.

4. Duration of ventilation: Time till mechanical ventilation was discontinued. This included weaning time.
5. Intermediate syndrome:

   Presence or absence of intermediate syndrome was assessed in each case according to the criterion laid down earlier.

6. Infections:

   Most common infections in these patients viz. Aspiration pneumonia, ventilator associated pneumonia, thrombophlebitis, blood stream infection, catheter related infections, skin and tracheostomy site infection and exposure keratitis was looked for in each patient.

7. Other hospital related morbidities like occurrence of acute renal failure, pancreatitis, hepatic dysfunction, arrythmias, cardiac arrest and atropine toxicity was also documented.

8. Mortality

   Death occurring due to any cause was considered to be directly or indirectly due to the poisoning.

Patients lost to follow up

These were patients who were taken away by the relatives due to monetary constraints, futility of the situation etc. These patients were counted as “dead” for the analysis.

MATERIALS AND METHODS PART II

A prospective clinical evaluation of a simple algorithm based treatment regimen for atropine administration in the treatment of acute organophosphate poisoned adults admitted to Christian Medical College Hospital Vellore for the treatment of acute organophosphate poisoning.

EVOLUTION OF THE PROTOCOL TO BE USED IN PART II OF THE STUDY.

The study protocol was based on the results of the data obtained in the part I study, also considering the literature recommendations and the feasibility in general practice.

The dose distribution was not similar between patients and there were major variations in atropine requirement among the patients treated. The dose requirement did not follow a normal bell shaped distribution curve. In order to prevent the skewed data from affecting the dose to be followed in the protocol standard deviation was considered not useful in deriving the dosing protocol using our data. The mean values and the total requirement were predominantly considered. The cumulative mean atropine requirement on day 1 was 60 mgs which decreased to 22.8 mgs on day 2, however the range varied from 0-256 mgs. Subsequent atropine requirements were minimal except for few patients. The atropine dosage did not follow a definite pattern and hence any statistically derived mathematical formula to predict the dose

requirement was not possible using our data. Based on the obtained data, considering the wide variation in requirement among individual patients and the maximum dose being 60 mgs on day 1, the following simple protocol was derived.

Intervention studied

The following protocol was defined and studied.

The patients were stabilized with the following regimen before atropine infusion protocol was initiated. This was done to ensure rapid stabilization.

Initial atropinisation protocol:

Inj Atropine sulphate 2 mg iv stat and double the dose and repeat every 5 minutes till Blood pressure > 90 systolic, Heart rate > 100 pm, no wheeze/crackles on auscultation

Atropine infusion protocol (Study protocol):

DAY 1:	Atropine infusion at	5 mg/hour x 2hrs
		4 mg/hour x 2 hrs
		3 mg/hour x 2 hrs
		2 mg/hour x 18hrs
DAY 2:	Atropine infusion at	2 mg/hour.
DAY 3:	Atropine infusion at	1 mg/hour.
DAY 4:	Atropine infusion at	0.5 mg/hour.

Prescribed deviation in the atropine dosing.

In case of a decline in heart rate to less than 100 bpm on day 1 and 60 bpm on day 2 onwards 1mg atropine intravenous boluses to be repeated every 3 minutes.

In case of persistent tachycardia HR > 120bpm atropine infusion can be lowered by 1 mg/hour.In case of persistent tachycardia HR > 120bpm atropine infusion can be lowered by 1 mg/hour.

All other supportive measures were given as required and the day to day decisions on management will be made by the concerned unit physician. Oximes like Pralidoxime (P2AM) were not used in the treatment.

Population studied:

Adult population (aged 12 years or older) with moderate to severe poisoning admitted to the emergency ward of Christian Medical College Hospital Vellore after definite history of organophosphate poisoning or with clinical evidence of organophosphate poisoning within 48 hours of poisoning.

The inclusion and exclusion criterion were the same as mentioned before for part I study.

Method of recruitment of patients for the evaluation of study regimen.

All consecutive patients with organophosphorus poisoning or clinically suspected organophosphorus poisoning who fulfilled the inclusion criterion, admitted to the Christian Medical college hospital Vellore between 1st

february 2006 and 15st August 2006 were enrolled into the study. Arrival of the patients was informed to researcher by the emergency unit staff on arrival. The initial management including stabilization and initial atropinisation was carried out by the emergency unit staff according to individual needs till the patient was enrolled into the study. All suitable patients were enrolled into the study as per the inclusion and exclusion criterion and further management was done according to the intervention protocol.

Method of implementation of the study protocol:

On arrival to the emergency room, the patients were screened and enrolled into the study. The stabilization was carried out in the emergency ward and patients were monitored using continous ECG monitor, pulse oximetry and blood pressure. Atropine boluses were used for the initial atropinisation. After achieving the target blood pressure and heart rate the patients were given planned atropine infusion as per the protocol.

Initially the atropine infusion was administered by using microdrip intravenous sets in the emergency room. Once stable, the patients were shifted to the ward or ICU. The instructions regarding the study protocol was documented for administration by the nursing staff and they were instructed regarding the same. In the ICU, patients were monitored continuously. In the event of bradycardia, patient was given atropine bolus dose by the nursing staff, to achieve the target heart rate as planned. The reason for change in the dose of atropine planned was documented. The infusion rate was decreased

in the event of a tachycardia. Vital parameters were recorded continuously in the ICU and at least hourly in the ward on the first day. The decision for intubation and shifting to ICU if required was taken by the treating physician. The patients were examined daily and the hourly dose administered, the hospital events and complications were documented by the researcher. Data was also collected from the inpatient hospital records. Patients were also examined regularly by the treating physicians and all the decisions regarding the daily management was taken by them. The decisions regarding duration of ventilation, tracheostomy and antibiotic usage was also decided by them.

The patients were assessed daily till discharge from the hospital.

Clinical assessment:

Daily assessment and documentation of the hourly atropine requirement, atropine toxicity, in hospital events, complications, onset of intermediate syndrome, and requirement for mechanical ventilation, tracheostomy and duration of mechanical ventilation were documented according to the clinical proforma (Appendix 2) by the investigator till the patient was discharged from the hospital for both parts of the study.

Assessment of severity of poisoning:

The severity of poisoning was assessed by the Namba scale[36] (appendix 1). The poisoned patients were divided into three categories, mild, moderate and severe. Only patients with moderate or severe poisoning were included in the study.

Assessment of the duration of the cholinergic crisis

This was defined by the duration of atropine use in days.

Diagnosis of intermediate syndrome:

Intermediate syndrome was defined as proximal muscle weakness of Grade 3 or less, 72 hrs after poisoning with or without requirement of mechanical ventilation.

Outcome measures

As mentioned previously for the part I study.

RESULTS – PART I

A total of 36 patients admitted to the Christian Medical college hospital Vellore between 1st September 2004 and 31st May 2005 with moderate to severe organophosphorus poisoning were enrolled in the study according to the inclusion criterion.

SEX DISTRIBUTION: There were 24 (66.7%) were males and 12 females. (Figure4).

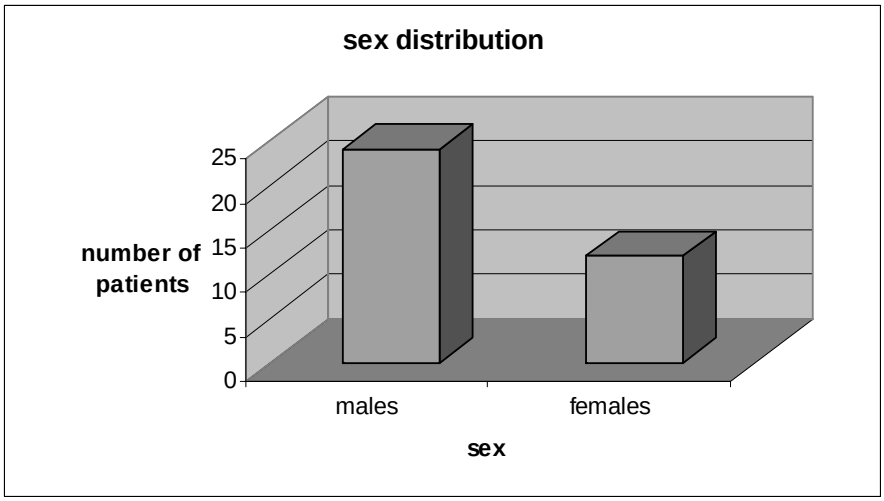


Figure 4: Sex distribution of the population studied.

AGE: The average age of the patients was 29.7 years (range 15 – 72 years) with 85% of our patients being less than 40 years old.

Age groups	Males n=24	Females n=12	Total n=36.
12-20 yrs	6	2	8
21-40 yrs	14	10	24
>40 yrs	4	0	4

Table 3: Age distribution of patients with OP poisoning.

PSYCHIATRIC EVALUATION:

In only 10 (27.8%) patients evaluation by a psychiatrist revealed any factors for which any specific treatment was needed , the rest of the suicide attempts were either accidental or due to an impulsive act secondary to an acute stress situation (Figure 5).

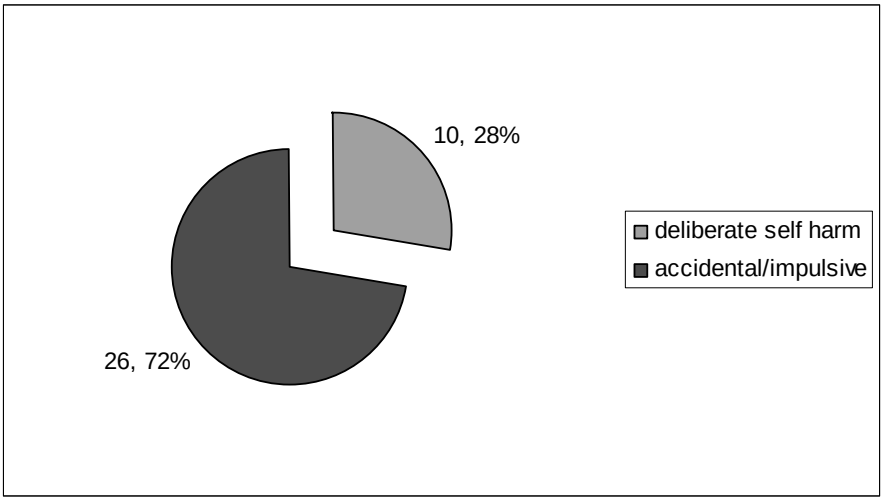


Figure 5: Reason for poisoning.

This emphasizes that suicidal attempts in most instances are due to an acute stress and the patient mostly leads a normal life after recovery.

CLINICAL FEATURES: The clinical features at admission are given in table.

Clinical findings	Number, total n=36	Percentage %
Miosis	20	55.6
Pulmonary secretions	19	52.8
Bradycardia	10	27.8
Hypertension	5	13.9
Crackles/wheeze	10	27.8
Required intubation at admission	15	41.7

Table 4: Clinical features at admission.

ATROPINE DOSING:

The atropine requirement of the patients during the first four days of there treatment is given below in Table5.

Atropine dose	Range(mgs)	Mean(mgs)	Std. Deviation	Median	Mode
hour 1	0-40	6.6	7.1	5	10
hour 2	0-36	3.6	8.5	1	0
hour 3	0-40	3.2	7.6	1	0
hour 4	0-16	2.0	3.7	1	0
hour 5	0-8	1.5	1.8	1	0
hour 6	0-10	1.4	2.1	1	0
hour 7	0-12	1.5	2.6	1	0
hour 8	0-12	1.6	2.4	1	0
hour 9	0-18	2.7	4.6	1	2
hour 10	0-12	1.7	2.3	1	1
hour 11	0-12	1.8	2.4	1.5	0
hour 12	0-12	1.9	2.4	1.5	2
hours 13TO24	0-144	30.6	36.7	21	0
DAY2	0-256	22.8	43.9	11	0
DAY3	0-222	11.0	37.1	0	0
DAY4	0-86	3.3	14.3	0	0

Table 5: Dose of atropine utilized in the treatment of acute organophosphate poisoning.

The mean total dose requirement of atropine for treatment on day 1 was 60 mgs. Figure shows the mean hourly requirement of atropine during the first 12 hours of treatment in the hospital.

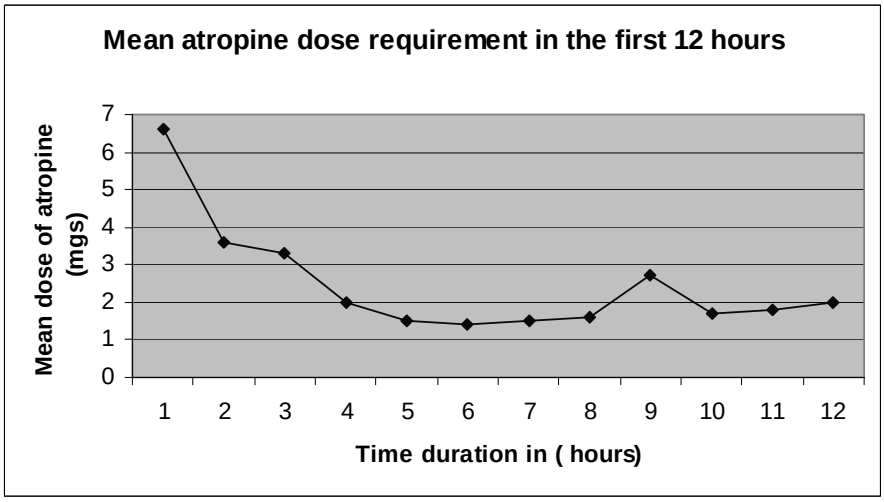


Figure 6: Atropine requirement in the first 12 hours.

The Following graph shows the mean atropine requirement over first four days of treatment after admission.

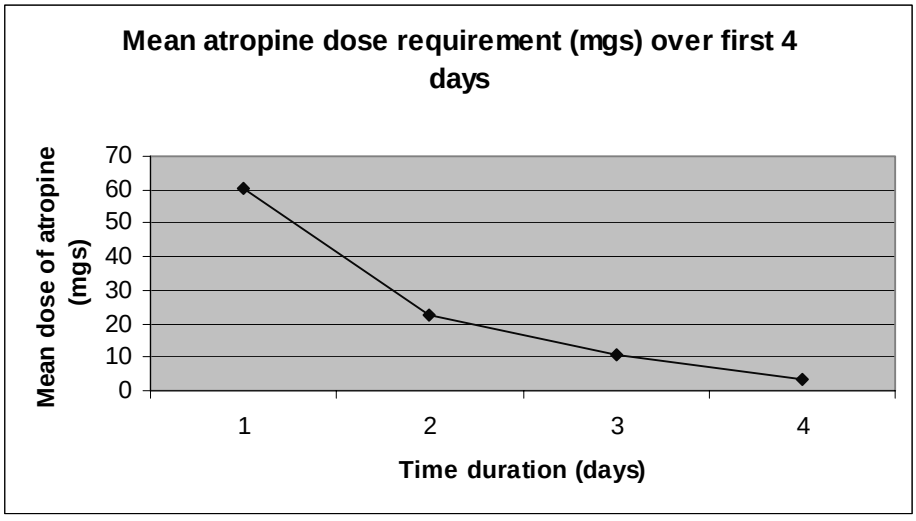


Figure7: Atropine requirement during first four days.

ATROPINE TOXICITY:

Only 3(8.3%) patients had atropine toxicity during the course of treatment in the hospital (Figure 8).

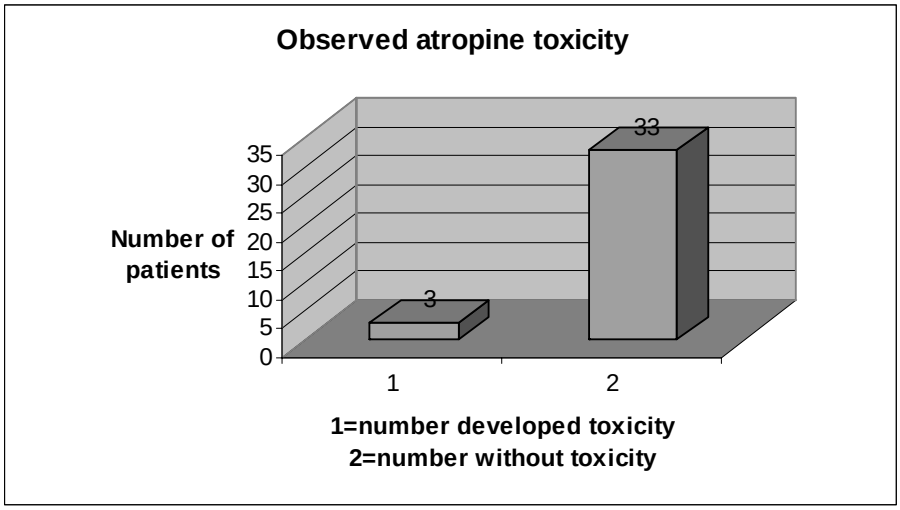


Figure8: Atropine toxicity observed during treatment.

PSEUDOCHOLINESTERASE LEVEL:

The mean pseudocholinesterase level at admission was 902.1(range 127-5850), Figure 9.

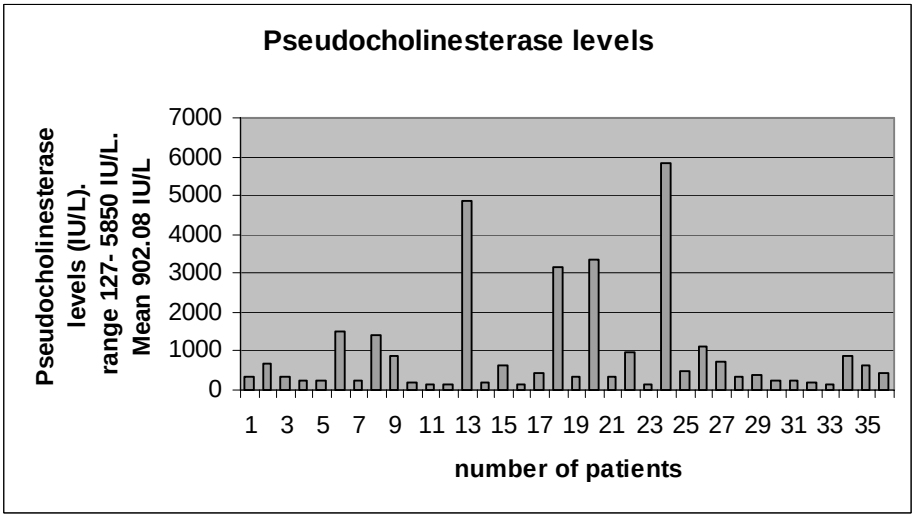


Figure 9: Pseudocholinesterase levels in individual patients.

INTERMEDIATE SYNDROME:

A total of 17(47.2%) patients developed intermediate syndrome, Figure 10.

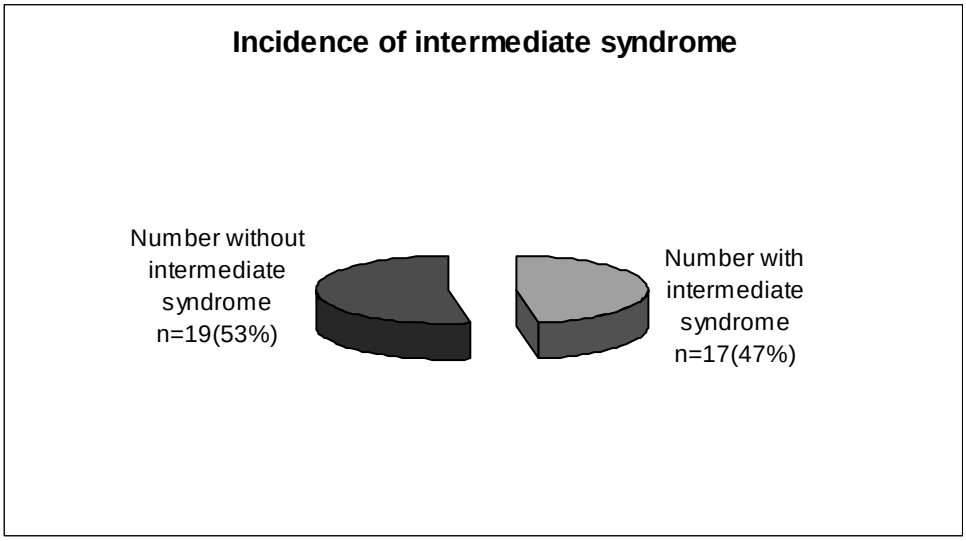


Figure 10: Incidence of intermediate syndrome.

ANTIBIOTIC USAGE:

The prevalence of use of antibiotics in the management of patients was 88.9% (n=32) and an infection most commonly respiratory or urinary was documented in 86% (n=31) of patients. The antibiotic use increased with increase in the hospital stay. Fever, leucocytosis is a common feature which occurs early in OP poisoning and does not necessarily mean an infection.

VENTILATION:

The mean duration of ventilation was 188.7 hours (range 0- 552, SD 165.99) Figure 11. The mean duration of ventilation among patients who developed intermediate syndrome was 319.1 hours and 65.2 hours in patients who did not develop intermediate syndrome.

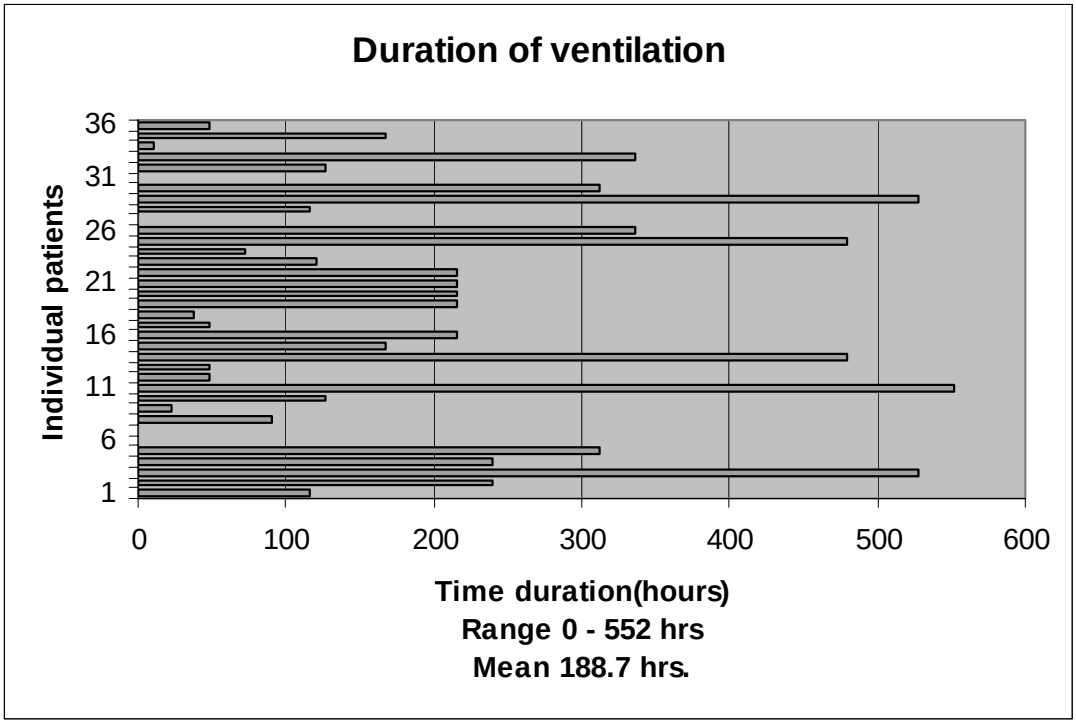


Figure 11: Duration of ventilation.

Once managed through the acute phase the patients with moderate and severe poisoning who develop intermediate syndrome usually require long duration of ventilation. Prolonged ventilation is the major cause for complications and its associated morbidity and mortality in addition to the cost burden.

MORTALITY:

The overall mortality due to organophosphate poisoning in the cases studied was 8.3 % (n=3), Figure 12.

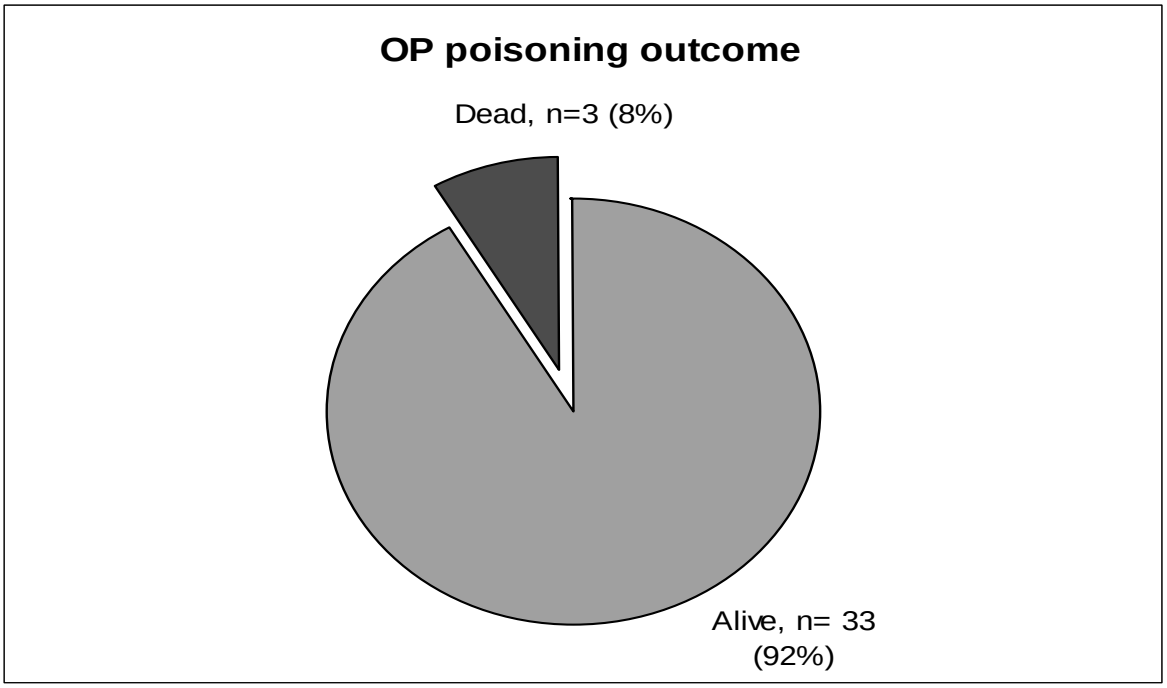


Figure 12: Mortality in organophosphorus poisoning.

The cause of death was due to cardiovascular collapse in the early cholinergic phase of poisoning in all patients.

RESULTS - PART II

A total of 104 patients who were admitted with poisoning to the Christian Medical College Hospital Vellore between 1st February 2006 and 15th August 2006 were screened for eligibility. A total of 58 patients were admitted due to insecticide poisoning. 42 admissions were due to organophosphorus poisoning. 25 patients with moderate to severe poisoning were included in the study after informed consent was taken. 15 patients with organophosphorus poisoning had only mild poisoning and hence were excluded. 2 patients were not enrolled due to failure to obtain informed consent from the family.

Baseline characteristics:

AGE & SEX

The mean age of patients was 26.8 years (range 15-66 yrs). There were 16(64%) males.

Age groups	Males n=16	Females n=9	Total n=25.
12-20 yrs	1	5	6
21-40 yrs	13	4	17
>40 yrs	2	0	2

Table 6: Age distribution of patient's in Part II study.

OP COMPOUND:

In only 12(48%) patients the exact compound ingested was known and only 4(16%) of patients were known to be poisoned by a dimethyl compound. On an average 80.52 ml was consumed by 19 people the amount consumed by the rest was not known.

PRE HOSPITALISATION TREATMENT:

14 (56%) patients presented to the hospital after gastric lavage at a local hospital.

About 36% of patients had received atropine in some form before admission to the hospital. Only 1(4%) patient had received treatment with pralidoxime before admission and 1 patient was intubated at a local hospital and referred here for further treatment.

CLINICAL FEATURES:

At admission to the emergency room the following were the baseline characteristics.

Features at admission	**Frequency**	**Percentage of total (n=25)**
Bradycardia	9	36 %
Hypotension	2	8 %
Miosis	18	72 %
Paradoxical respiration	11	44 %
Seizures	1	4 %
Electrolyte abnormality	13	52 %
Tachycardia	6	24 %
Hypertension	2	8 %
Mydriasis	0	0 %
Respiratory arrest	3	12 %
Acute renal failure	1	4 %
Aspiration pneumonia	3	12 %
Tachypnea	13	52 %
leucocytosis	11	44 %
Pre admission gastric lavage	14	56%
Pre admission treatment with atropine	9	36%
Pre admission oxime treatment	1	4%
Intubation before admission	1	4%

Table 7: Baseline clinical characteristics at enrollment.

GCS AT ADMISSION:

The following graph depicts the GCS (Glasgow Coma Scale) score for all the patients enrolled into the study at admission.

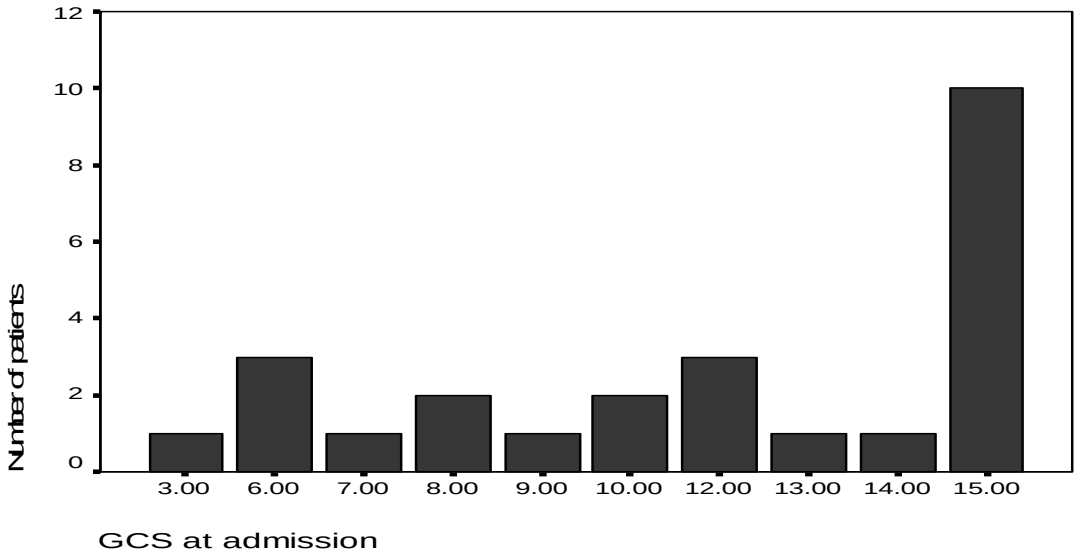


Figure 14: GCS scores of patients at admission to hospital.

PSEUDOCHOLINESTERASE LEVELS: The mean pseudocholinesterase level was 570.2 IU/L (range 190-3459 IU/L, SD 628.6).

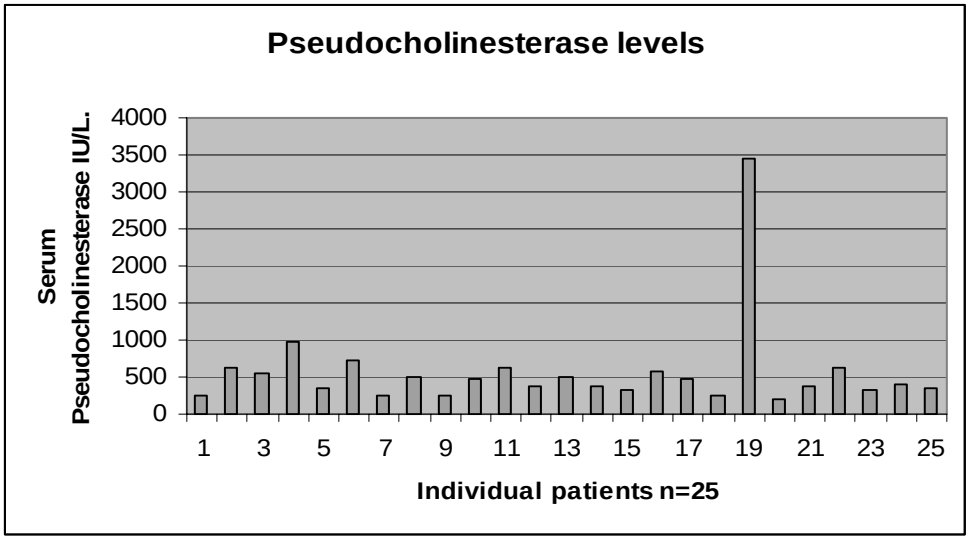


Figure 15: Pseudocholinesterase levels at admission in study patients.

INTERMEDIATE SYNDROME: Intermediate syndrome developed in 10(40%) of patients. The mean onset time for the development of intermediate syndrome was 4.1 days (range 1-7 days, SD 2.02).

INITIAL ATROPINISATION:

The mean atropine required for intial atropinisation of a patient was 8.88 mg (range 0-34mg, SD 9.12). The bar diagram below shows the required doses for initial atropinisation in all 25 patients enrolled into the study.

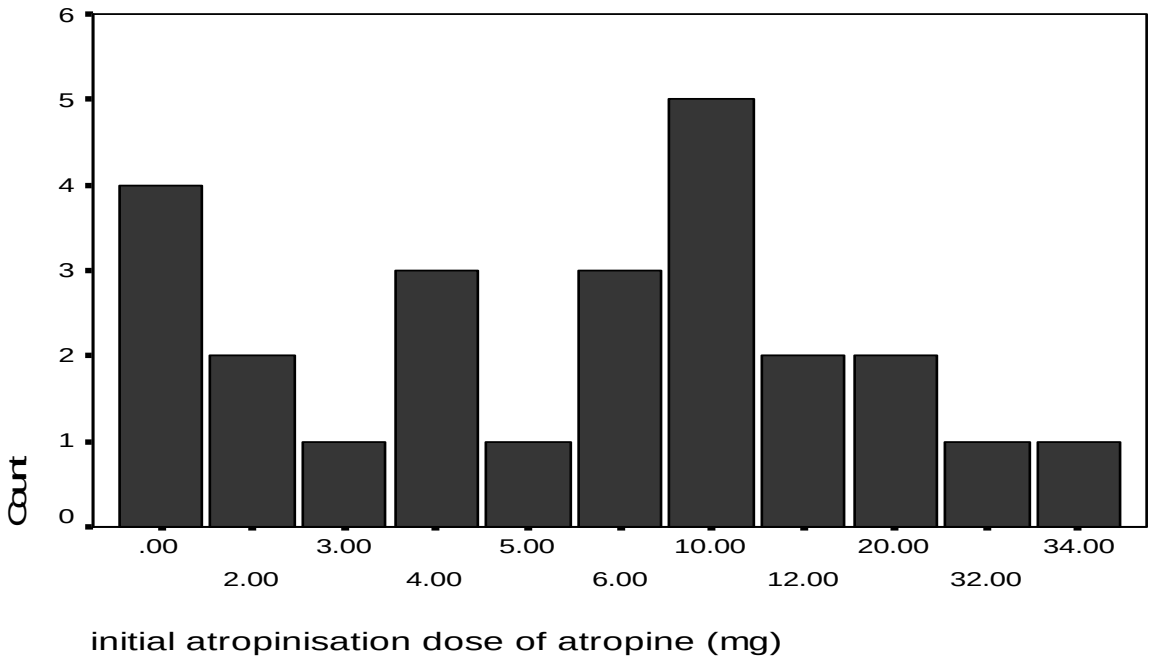


Figure 16: Dose of atropine (mgs) required for initial atropinisation.

PROTOCOL VIOLATIONS: The numbers of patients deviating from the protocol (either needing more or less than planned dose) were taken as protocol violations. The data is given in the table 8.

Timing	Planned dose of atropine (mg)	Number stable on the planned dose.	Number of protocol violation.	Number requiring more than planned dose.
0-2 hrs	10	21(84%)	4	1(4%)
3-4 hrs	8	16(64%)	9	3(12%)
5-6 hrs	6	13(52%)	12	5(20%)
7-8 hrs	4	16(64%)	9	7(28%)
9- 24hrs	32	13(52%)	12	6(24%)
Day 1	60	5(20%)	19	9(36%)
Day2	48	7(28%)	17	6(24%)
Day 3	24	4(16%)	20	4(16%)
Day4	12	2(8%)	18	3(12%)

Table 8: Patient's deviating from the protocol, during treatment with fixed planned regimen of atropine.

The number of protocol violations increased with time and the initially planned dose was not unacceptable in a significant number of patients beyond 6-8 hours. However the number of patients which needed more than the planned dose (clinically more important) were less, compared to the people who needed less than the planned dose.

The following were the reasons for protocol violations in the group of patients studied.

Timing	**Number of protocol violation n=25**	**Number requiring more than planned dose.**	**Reasons for protocol violation**			
			Control of heart rate	**Reduce secretions**	**Low blood pressure**	**Cardiac arrest**
0-2 hrs	4	1				1
3-4 hrs	9	3	1	2		
5-6 hrs	12	5	3	1	1	
7-8 hrs	9	7	9			
9- 24hrs	12	6	5			1
Day 1	19	9	9			
Day2	17	6	5		1	
Day 3	20	4	4			
Day4	18	3	3			

Table 9: Causes for increased atropine requirement and time of occurrence.

Timing	Number of protocol violation n=25	Number requiring less than planned dose.	Reasons for protocol violation			
			Control of heart rate	pyrexia	confusion	Urinary retention
0-2 hrs	4	3	3			
3-4 hrs	9	6	4			2
5-6 hrs	12	7	5	1	1	
7-8 hrs	9	2	2			
9- 24hrs	12	6	4		2	1
Day 1	19	10	3	1	3	3
Day2	17	11	11			
Day 3	20	16	16			
Day4	18	15	15			

Table 10: Causes for decreased atropine requirement and time of occurrence.

OUTCOMES:

A total of 16 (64%) patients needed mechanical ventilation during the treatment. The mean duration of ventilation was 10.87 days (range 1-21 days, SD6.69).

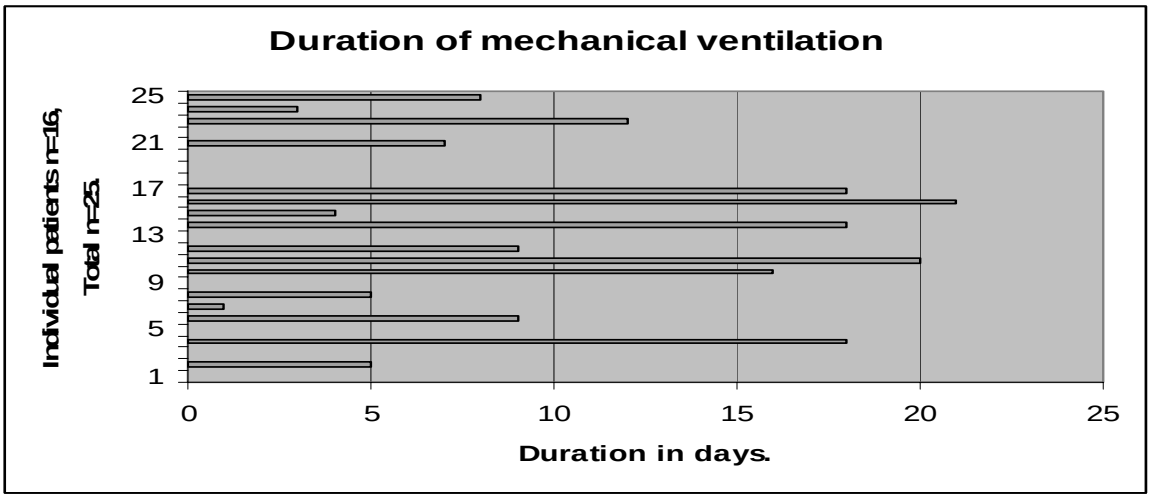


Figure 17: Duration of mechanical ventilation during treatment.

Tracheostomy was performed on 9(36%) of patients and the mean day of performing tracheostomy from admission was 6.78 days (range 5-10 days, SD 1.48).

The mean duration of hospital stay was 11.08 days (range 1-28 days, SD 8.61).

MORTALITY

Total of 22 (88%) of patients survived and were discharged in a normal state. The all cause mortality related to poisoning was 12%.

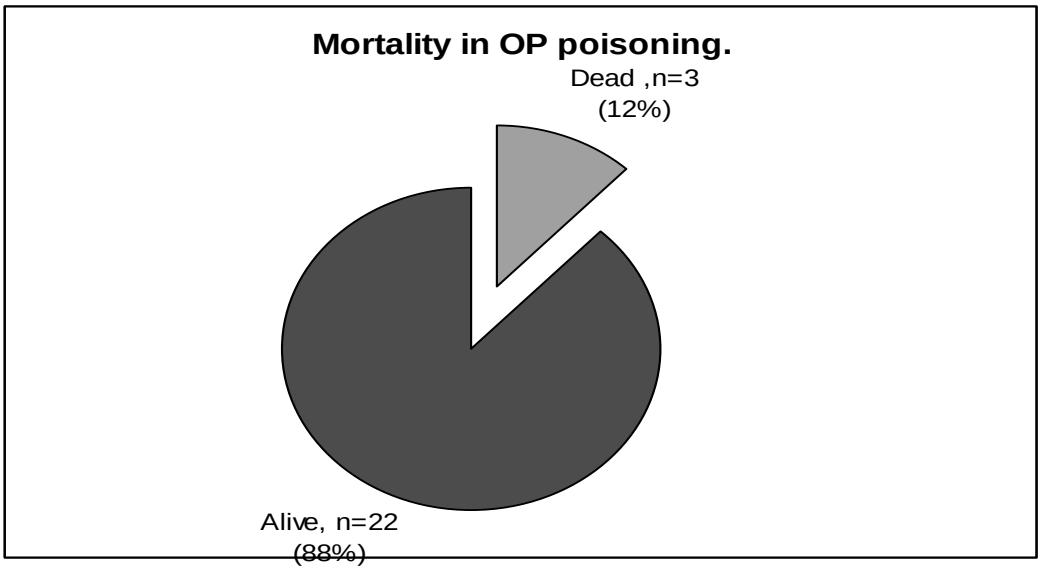


Figure 18: Mortality in the treatment of acute OP poisoning.

COMPLICATIONS:

The following complications were observed during the treatment in the hospital.

In hospital complications	Frequency	Percentage of total
Cardiac arrest	5	20 %
Hypotension	4	16 %
Aspiration pneumonia	9	36 %
Nosocomial pneumonia	7	28 %
Septicemia	2	8 %
Acute renal failure	1	4 %
Hepatic dysfunction	0	0 %
Pancreatitis	0	0 %
Atropine toxicity	2	8 %
Mechanical ventilation	16	64%

Table11: Complications during treatment in hospital.

During the treatment period after initial atropinisation and stabilization, when the atropine infusion was given as per the fixed protocol and patient's heart rate, blood pressure, wheeze, secretions were closely monitored.

ATROPINE TOXICITY: Atropine toxicity was noticed in only 2(8%) of the patients treated with the regimen.

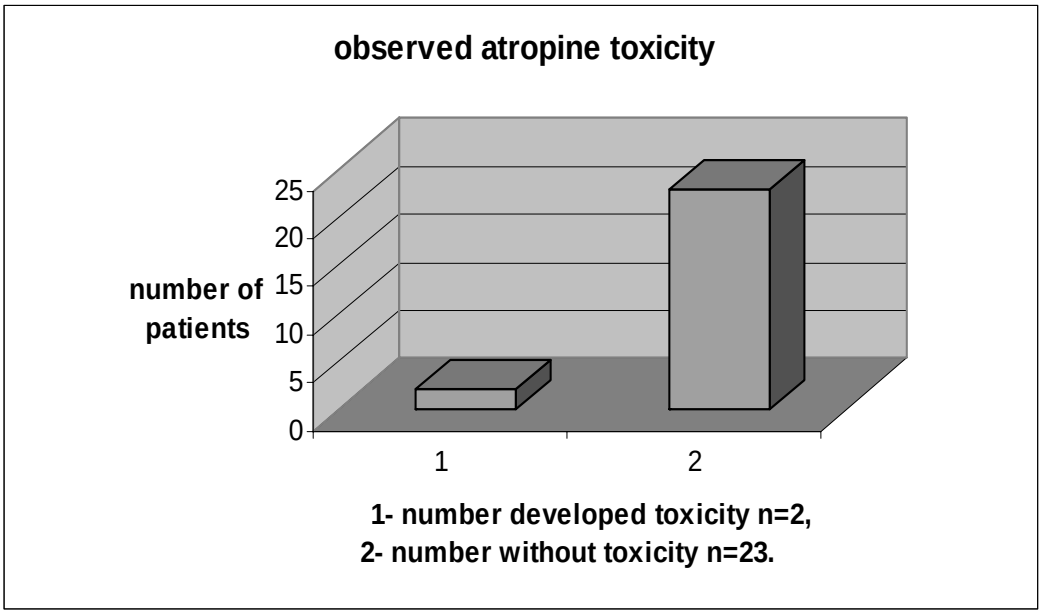


Figure 19: Development of atropine toxicity on treatment.

The low incidence of atropine toxicity is due to usage of low doses in our infusion protocol and also prompt reduction in the dose required if needed due to regular monitoring.

DISCUSSION

Published literature is very sparse in the area of guidelines for adequate atropinisation in OP poisoning. Over several years the department of medicine at Christian medical college hospital, Vellore has found that keeping the heart rate at or around 100 beats per minute and ensuring absence of crackles on lung auscultation, are the two most important end points for adequate atropinisation. Pupillary size and assessment of central nervous stimulation have not been found useful (unpublished communication). Therefore heart rate and crackles were used as the main indicators of adequate atropinisation, in this study.

The results of the observational study (Part 1), indicates that the cumulative mean dose of atropine used in the first 24 hours was 60 mgs. This dose is significantly less than the published recommendations. A perusal of individual values shows a very wide range of doses, and the values do not show a Gaussian distribution. Therefore the median and mode values were considered, and these indicated very small doses.

The atropine doses recommended in the published literature are not comprehensively stated. The doses mentioned seem to indicate the initial high doses needed for the first 8 to 12 hours. If the recommended doses are extrapolated over a 24 hour period then most recommendations would advocate doses of 192 mgs to more than 1000 mgs. It is clear from PART 1 of this study that in fact much smaller doses are required. Only 9 cases needed more than 65 mgs over 24 hours.

A study of atropine pharmaco-kinetics cannot be expected to be helpful in formulating a dosing protocol. This is partly because drug distribution in body compartments cannot predict how much drug will inhibit the cholinergic receptors which are being overstimulated by an unknown dose of acetylcholine esterase inhibitor. Earlier studies have not shown correlation of pseudo cholinesterase levels of mortality, or severity of illness, but are helpful in diagnosis.

For the above reasons it was decided to use the data obtained in part I to formulate the algorithm to be used in Part II.A decremental pattern was chosen as the study indicated that higher doses were needed initially, and smaller doses were required subsequently. A total of 60 mg per day was used as guided by Part 1 results, followed by decreasing doses. The results obtained in Part II shows that the protocol was successful in the first 24 hours of the study, wherein majority of the patients did not need excess atropine than planned. However from the 24 hour onwards, more number of patients needed dose adjustment. A major achievement was rapid atropinisation. The maximum atropine required to stabilize patient initially before the infusion was begun was 34 mgs. This amount was administered within 15-20 minutes after arrival as per the protocol. The results show that some fine-tuning of the algorithm needs to be done, and retested to see if it is more suitable. This study shows that a protocol based dose regimen of atropine may be useful in the early management of organophosphorus poisoning. As time passes by the patients requirement are different and difficult to predict, probably due to the

different load of poison taken, different built, body fat content and the type of poison taken.

It is possible that no algorithm will be effective for all patients, but one which is efficacious 80% of the time, will be a great advance. More study is needed to see if the dose of atropine varies according to the compound used and the dose of the poison ingested .The reasons for persisting with finding a suitable algorithm are very cogent. An easy to follow algorithm allows freeing up of skilled nursing time especially in secondary care centers where nurses and doctors may be in short supply, or engaged in looking after other ill patients.

Atropine toxicity is common if high doses as recommended in literature are given for many hours without supervision. While high doses ensure that no death occurs due to bradyarrythmias, there is a high incidence of intense central nervous system stimulation. This is very detrimental as it causes dehydration, hyperpyrexia, severe restlessness, and possibly results in increased mortality. In both parts of the study, the atropine toxicity was found to be very low.

The mortality in part 1 was 8.33 % and in the second was slightly though not significantly higher at 12%. The study was not designed to compare mortality as an outcome. It can be inferred however that use of the algorithm did not cause a detrimental effect of increased mortality.

In this study a control arm was not studied in Part II. The reason for this was that this was an efficacy and safety study designed to show that an algorithmic approach is feasible and does not increase toxicity and other complications. However to compare outcomes like mortality the best study design would be a randomised controlled trial comparing the protocol with the current practice. This study proves safety and efficacy in early stages. Further study should be done as a double blind randomized controlled trial to compare an algorithmic dosing schedule, to an individualized dosing pattern.

CONCLUSION

The results of this study shows the following-

1. Administration of atropine using a fixed algorithm is easy and effective in administring the atropine requirement in the management of early phase of acute organophosphorus poisoning.
2. Smaller doses of atropine are sufficient in treating cases of OP poisoning, than those recommended in literature. This resulted in less atropine toxicity, without increasing complications.
3. More studies are required to predict and study causes of wide variability in atropine requirements.

LIMITATIONS

1. The study is done on a small number of patients.

2. The study was not designed to compare outcomes such as mortality.

3. Many patients enrolled into the study were referred from a peripheral hospital and treatment received there might have had some influence on the requirement of atropine.

4. All patients did not receive the same standard of care as some of them were managed in the general wards due to non availability of beds in the ICU.

5. The study involved only the moderate to severe organophosphorus poisoned patients. Many of them requiring mechanical ventilation were also sedated, this may have had masked the mild features of atropine toxicity.

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APPENDIX-I

Severity grading of organophosphorus poisoning by Namba et al [36]

Severity score	symptoms	Serum BuChE levels (%)
Mild	Dizziness, nausea, vomiting, diarrhea, abdominal pain, salivation and wheezing.	20 – 50 %
Moderate	All of the above and weakness, inability to walk, fasciculations, dysarthria, miosis.	10 – 20 %
Severe	All of the above and coma, flaccid paralysis, pulmonary edema, respiratory distress.	< 10 %

Organo phosphorus poisonoing study(Part I) data collection sheet.

Hospital number

Sex

Age

Compound

Known psychiatric illness

Time gap at presentation

CLINICAL FEATURES

Miosis

Bronchorrhea

Micturition

Diarrhea

Bradycardia

Hypotension

Crackles

Intubation at admission

ATROPINE DOSE (mg)

Day 1	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-11	11-12	12-24
Atropine dose infusion													
Additional													
Total													

	Day 1	Day 2	Day 3	Day 4
Infusion				
Additional				
Total				

Atropine toxicity Y/N , HR- , Dose of atropine

Pseudocholinesterase

Intermediate syndrome

Duration of ventilation

Time to regain consiousness

Complications

Antibiotics used

Infection - UTI / LRI / LINE

Fever

Premorbid condition-

Outcome -- alive / dead.

Data abstraction form – Organophosphate poisoning study
PATIENT SERIAL NUMBER:

Name: Hospital Number:
Age: Sex: State:

Name of Pesticide: Type: Dimethyl / Diethyl / Unknown
Amount consumed(ml) : Source:
Date/Time of consumption:

Pre-hospital treatment:
Gastric lavage given: Yes / No Atropine: Yes / No
Oximes: Yes / No If yes dose: Time given:
Cardiac/Respiratory arrest: Yes / No Ventilation: Yes / No

At admission: (Circle features present at admission)

Bradycardia	Tachycardia	Arrhythmia
Hypotension	Hypertension	Ventricular Fib
Miosis	Mydriasis	Tachypnea
Paradoxical respiration	Respiratory arrest	Aspiration pneumonia
Seizures	Acute renal failure	Leukocytosis
Electrolyte abnormality	GCS	Pseudo chol

In hospital data (circle features observed)

Cardiac arrest	Arrhythmias	Hypotension
Ventricular fibrillation	Aspiration pneumonia	Nosocomial pneumonia
Nosocomial UTI	Septicaemia	Acute renal failure
Hepatic dysfunction	Pancreatitis	Atropine toxicity

Organisms identified & site:

Days	1	2	3	4	5	6	7
Atropine dose planned (mg)							
Additional dose							
Total dose							

Day1	0-2 hrs	3-4 hrs	5-6 hrs	7-8 hrs	9-24 hrs
Atropine dose planned (mg)					
Additional dose					
Total dose					

Intermediate syndrome: Yes / No If yes onset time:
Ventilation: Yes / No If yes duration (days):
Tracheostomy: Yes / No If yes day of tracheostomy (after poisoning):

Duration of ICU stay (days): Duration of hospital stay (days):

ICU outcome: Dead / Alive / Discharged at request/ PVS
Hospital outcome: Dead / Alive / Discharged at request / PVS

Total cost (Rs):

Appendix 6: Key to data sheet part I

VARIABLE	EXPANSION	CODE 1	CODE 2	VALUE
sex	sex	Male	Female	
age	age			years
psyill	psychiatry illness	Present	Absent	
miosis	miosis at admission	Present	Absent	
pulmsec	pulmonary secretions at	Present	Absent	
brady	admission	Present	Absent	
hypotens	bradycardia at admission	Present	Absent	
crackles	hypotension at admission	Present	Absent	
admintub	crackles at admission	Yes	No	
atrhr1	intubated at admission			mgs
atrhr2	atropine requirement hour 1			mgs
atrhr3	atropine requirement hour 2			mgs
atrhr4	atropine requirement hour 3			mgs
atrhr5	atropine requirement hour 4			mgs
atrhr6	atropine requirement hour 5			mgs
atrhr7	atropine requirement hour 6			mgs
atrhr8	atropine requirement hour 7			mgs
atrhr9	atropine requirement hour 8			mgs
atrhr10	atropine requirement hour 9			mgs
atrhr11	atropine requirement hour 10			mgs

atrhr12	atropine requirement hour 11			mgs
at13to24	atropine requirement hour 12			mgs
atrday2	atropine requirement hour 13 to			mgs
atrday3	24			mgs
atrday4	atropine requirement day 2			mgs
atrtox	atropine requirement day 3	Develope	Not developed	
pseudoch	atropine requirement day 4	d		IU/L
intsynd	atropine toxicity		Not developed	
durvent	pseudocholinesterase at	Develope		Hours
concious	admission	d		Hours
antibiot	intermediate syndrome		No	
infectio	duration of ventilation		No	
fever	time to regain consiousness	Yes	No	
premorbi	antibiotic used	Yes	Absent	
outcome	infections developed	Yes	Dead	
	fever in hospital	Present		
	premorbid illness	Alive		
	hospital outcome			

Appendix 7: Key to data sheet part II

VARIABLE	EXPANSION	CODE 1	CODE 2	VALUE
name	name			Name
hospno	hospital number			Number
age	age			Years
sex	sex			
opclass	organophosphorus class	Male	Female	
amount	amount consumed (ml)	Dimethyl	Diethyl	
glavage	gastric lavage			ml
atropine	pre hospital atropine treatment			
oximes	pre hospital oximes treatment	Yes	No	
arrest	prehospital cardiac/respiratory arrest	Yes	No	
ventilat	pre hospital ventilation	Yes	No	
brady	bradycardia at admission	Yes	No	
hypotens	hypotension at admission	Yes	No	
miosis	miosis at admission	Yes	No	
paradoxb	paradoxical respiration at admission	Yes	No	
seizures	seizures at admission	Yes	No	
electrol	electrolyte abnormality at admission	Yes	No	
tachycar	tachycardia at admission	Yes	No	
hyperten	hypertension at admission	Yes	No	
mydriasi	mydriasis at admission	Yes	No	
resparre	respiratory arrest at admission	Yes	No	
arf	acute renal failure at admission	Yes	No	
gcs	GCS at admission	Yes	No	
arrythmi	arrythmia at admission			
vfib				
tachypne				
aspirati				

leucocyt	ventricular fibrillation	Yes	No	
pseudoch	tachypnea at admission	Yes	No	
hcardarr	aspiration pneumonia at admission			
hvfib	leucocytosis at admission			3 -15
huti	pseudocholinesterase at	Yes	No	
hhepdys	admission	Yes	No	
harryth	cardiac arrest in hospital			
haspirat	ventricular fibrillation in hospital	Yes	No	
hsepsis	nosocomial UTI	Yes	No	
hpancrea	hepatic dysfunction in hospital	Yes	No	
hhypoten	arrythmias in hospital			
hpneumon	aspiration pneumonia in hospital			IU/L
harf	septicaemia in hospital	Yes	No	
hatrtox	pancreatitis in hospital	Yes	No	
organism	hypotension in hospital			
siteorg	nosocomial pneumonia	Yes	No	
	acute renal failure in hospital	Yes	No	
	atropine toxicity in hospital	Yes	No	
	organism identified			
	site of infection	Yes	No	
		Yes	No	
		Yes	No	
		Yes	No	
		Yes	No	
		Yes	No	Name
		Yes	No	Site

VARIABLE	EXPANSION	CODE 1	CODE 2	VALUE
iniatrop	initial atropinisation dose of			mgs
hr1to2	atropine			mgs
hr3to4	atropine requirement hour 0-2			mgs
hr5to6	atropine requirement hour 3-4			mgs
hr7to8	atropine requirement hour 5-6			mgs
hr9to24	atropine requirement hour 7-8			mgs
day1	atropine requirement hour 9-24			mgs
day2	total atropine requirement day 1			mgs
day3	total atropine requirement day 2			mgs
day4	total atropine requirement day 3			mgs
intsyn	total atropine requirement day 4	Yes	No	
onsettim	developed intermediate syndrome			days
hventila	onset time for intermediate	Yes	No	
ventdur	syndrome			days
trach	ventilation requirement	Yes	No	
trachday	duration of ventilation			days
duricu	tracheostomy done			days
durhosp	day of tracheostomy after			days
icuoutco	poisoning	Alive	Dead	
houtcome	duration of ICU stay	Alive	Dead	
	duration of hospital stay			
	ICU outcome			
	hospital outcome			